



\* \* \* \* \*

=> s (hiv or aids or hiv(1)) (P) (cd28)

8087 HIV  
85130 AIDS  
8087 HIV  
2501795 1  
262 CD28  
L1 36 (HIV OR AIDS OR HIV(W)1) (P) (CD28)

=> s 11(P) (antibod?)

36705 ANTIBOD?  
L2 21 L1(P) (ANTIBOD?)

=> d 12 1-21 date

L2: 1 of 21

TITLE: CTLA4 receptor and uses thereof  
US PAT NO: 5,885,796 DATE ISSUED: Mar. 23, 1999  
[IMAGE AVAILABLE]  
APPL-NO: 08/465,078 DATE FILED: Jun. 5, 1995  
REL-US-DATA: Division of Ser. No. 375,390, Jan. 18, 1995, which is a  
continuation-in-part of Ser. No. 228,208, Apr. 15, 1994,  
which is a continuation-in-part of Ser. No. 8,898, Jan.  
22, 1993, which is a continuation-in-part of Ser. No.  
723,617, Jun. 27, 1991, abandoned.

L2: 2 of 21

TITLE: CTLA4 receptor and uses thereof  
US PAT NO: 5,885,579 DATE ISSUED: Mar. 23, 1999  
[IMAGE AVAILABLE]  
APPL-NO: 08/889,666 DATE FILED: Jul. 8, 1997  
REL-US-DATA: Division of Ser. No. 375,390, Jan. 18, 1995, which is a  
continuation-in-part of Ser. No. 228,208, Apr. 15, 1994,  
which is a continuation-in-part of Ser. No. 8,898, Jan.  
22, 1993, Pat. No. 5,770,197, which is a  
continuation-in-part of Ser. No. 723,617, Jun. 27, 1991,  
abandoned.

L2: 3 of 21

TITLE: CD9 antigen peptides and antibodies thereto  
US PAT NO: 5,883,223 DATE ISSUED: Mar. 16, 1999  
[IMAGE AVAILABLE]  
APPL-NO: 08/453,925 DATE FILED: May 30, 1995  
REL-US-DATA: Division of Ser. No. 253,751, Jun. 3, 1994, Pat. No.  
5,858,358, which is a continuation-in-part of Ser. No.  
73,223, Jun. 4, 1993, abandoned, which is a  
continuation-in-part of Ser. No. 200,247, Feb. 23, 1994,  
abandoned, which is a continuation-in-part of Ser. No.  
864,805, Apr. 7, 1992, abandoned, which is a  
continuation of Ser. No. 247,505, May 23, 1994,  
abandoned, which is a continuation of Ser. No. 864,866,  
Apr. 7, 1992, abandoned, which is a continuation of Ser.  
No. 218,155, Mar. 25, 1994, abandoned, which is a  
continuation of Ser. No. 864,807, Apr. 7, 1992,  
abandoned, which is a continuation-in-part of Ser. No.  
902,647, Jun. 19, 1992, abandoned, which is a  
continuation of Ser. No. 275,433, Nov. 23, 1988,  
abandoned, and a continuation-in-part of Ser. No.  
73,223, Jun. 4, 1993, abandoned.

L2: 4 of 21

TITLE: Suppressor of HIV replication and transcription

US PAT NO: 5,861,490 DATE ISSUED: Jan. 19, 1999  
[IMAGE AVAILABLE]  
APPL-NO: 08/471,430 DATE FILED: Jun. 6, 1995  
REL-US-DATA: Continuation-in-part of Ser. No. 38,387, Mar. 29, 1993,  
Pat. No. 5,627,023.

L2: 5 of 21

TITLE: Methods for selectively stimulating proliferation of T cells  
US PAT NO: 5,858,358 DATE ISSUED: Jan. 12, 1999  
[IMAGE AVAILABLE]  
APPL-NO: 08/253,751 DATE FILED: Jun. 3, 1994  
REL-US-DATA: Continuation-in-part of Ser. No. 73,223, Jun. 4, 1993,  
abandoned, Ser. No. 200,947, May 23, 1994, abandoned,  
Ser. No. 247,505, May 23, 1994, abandoned, and Ser. No.  
218,155, Mar. 25, 1994, abandoned, which is a  
continuation of Ser. No. 864,807, Apr. 7, 1992,  
abandoned, said Ser. No. 200,947 is a continuation of  
Ser. No. 864,805, Apr. 7, 1992, abandoned, said Ser. No.  
247,505 is a continuation of Ser. No. 864,866, Apr. 7,  
1992, each Ser. No. is a continuation of Ser. No.  
902,467, Jun. 16, 1992, abandoned.

L2: 6 of 21

TITLE: Soluble CTLA4 molecules and uses thereof  
US PAT NO: 5,851,795 DATE ISSUED: Dec. 22, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/459,818 DATE FILED: Jun. 2, 1995  
REL-US-DATA: Division of Ser. No. 375,390, Jan. 18, 1995, which is a  
continuation-in-part of Ser. No. 228,208, Apr. 15, 1994,  
which is a continuation-in-part of Ser. No. 8,898, Jan.  
22, 1993, which is a continuation-in-part of Ser. No.  
723,617, Jun. 27, 1991, abandoned.

L2: 7 of 21

TITLE: HIV matrix protein tyrosine position 29 pocket binders  
US PAT NO: 5,849,793 DATE ISSUED: Dec. 15, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/911,883 DATE FILED: Aug. 15, 1997

L2: 8 of 21

TITLE: CTLA4 Ig fusion proteins  
US PAT NO: 5,844,095 DATE ISSUED: Dec. 1, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/375,390 DATE FILED: Jan. 18, 1995  
REL-US-DATA: Continuation-in-part of Ser. No. 69,693, May 28, 1993,  
abandoned, and Ser. No. 228,208, Apr. 15, 1994, which is  
a continuation-in-part of Ser. No. 8,898, Jan. 22, 1993,  
which is a continuation-in-part of Ser. No. 723,617,  
Jun. 27, 1991, abandoned, said Ser. No. 69,693 is a  
continuation of Ser. No. 723,617.

L2: 9 of 21

TITLE: Methods for enriching specific cell-types by density  
gradient centrifugation  
US PAT NO: 5,840,502 DATE ISSUED: Nov. 24, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/299,467 DATE FILED: Aug. 31, 1994

L2: 10 of 21

TITLE: Method of inducing a cell to proliferate using a chimeric  
receptor comprising janus kinase  
US PAT NO: 5,837,544 DATE ISSUED: Nov. 17, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/485,293 DATE FILED: Jun. 7, 1995  
REL-US-DATA: Continuation of Ser. No. 382,846, Feb. 3, 1995.

L2: 11 of 21  
TITLE: Suppressor HIV-1 replication and transcription  
US PAT NO: 5,814,519 DATE ISSUED: Sep. 29, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/488,527 DATE FILED: Jun. 7, 1995  
REL-US-DATA: Division of Ser. No. 471,430, Jun. 6, 1995, which is a  
continuation-in-part of Ser. No. 38,387, Mar. 29, 1993,  
Pat. No. 5,627,023.

L2: 12 of 21  
TITLE: HIV nuclear localization inhibitors  
US PAT NO: 5,808,068 DATE ISSUED: Sep. 15, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/912,076 DATE FILED: Aug. 15, 1997

L2: 13 of 21  
TITLE: Monoclonal antibodies and FV specific for CD2 antigen  
US PAT NO: 5,807,734 DATE ISSUED: Sep. 15, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/456,221 DATE FILED: May 31, 1995  
REL-US-DATA: Division of Ser. No. 68,946, May 25, 1993.

L2: 14 of 21  
TITLE: Monoclonal antibodies and FV specific for CD2 antigen  
US PAT NO: 5,795,572 DATE ISSUED: Aug. 18, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/068,946 DATE FILED: May 25, 1993

L2: 15 of 21  
TITLE: Methods for regulating the immune response using B7  
binding molecules and IL4-binding molecules  
US PAT NO: 5,770,197 DATE ISSUED: Jun. 23, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/008,898 DATE FILED: Jan. 22, 1993  
REL-US-DATA: Continuation-in-part of Ser. No. 723,617, Jul. 27, 1991,  
abandoned.

L2: 16 of 21  
TITLE: Diagnostic test for replicative senescence in T cells  
US PAT NO: 5,744,317 DATE ISSUED: Apr. 28, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/755,291 DATE FILED: Nov. 22, 1996  
REL-US-DATA: Continuation of Ser. No. 307,508, Sep. 16, 1994,  
abandoned.

L2: 17 of 21  
TITLE: Chimeric receptors comprising janus kinase for regulating  
cellular proliferation  
US PAT NO: 5,741,899 DATE ISSUED: Apr. 21, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/481,003 DATE FILED: Jun. 7, 1995  
REL-US-DATA: Continuation of Ser. No. 382,846, Feb. 2, 1995.

L2: 18 of 21  
TITLE: Chimeric receptor molecules for delivery of co-stimulatory  
signals  
US PAT NO: 5,712,149 DATE ISSUED: Jan. 27, 1998  
[IMAGE AVAILABLE]  
APPL-NO: 08/383,749 DATE FILED: Feb. 3, 1995

L2: 19 of 21  
TITLE: Immunoglobulin superantigen binding to gp 120 from HIV  
US PAT NO: 5,691,135 DATE ISSUED: Nov. 25, 1997  
[IMAGE AVAILABLE]  
APPL-NO: 08/306,116 DATE FILED: Sep. 14, 1994

REL-US-DATA: Continuation-in-part of Ser. No. 259,669, Jun. 14, 1994,  
abandoned, which is a continuation of Ser. No. 9,705,  
Jan. 26, 1993, abandoned.

L2: 20 of 21

TITLE: Chimeric receptor molecules for delivery of co-stimulatory  
signals  
US PAT NO: 5,686,281 DATE ISSUED: Nov. 11, 1997  
[IMAGE AVAILABLE]  
APPL-NO: 08/455,860 DATE FILED: May 31, 1995  
REL-US-DATA: Continuation of Ser. No. 383,749, Feb. 3, 1995.

L2: 21 of 21

TITLE: Chimeric CTLA4 receptor and methods for its use  
US PAT NO: 5,434,131 DATE ISSUED: Jul. 18, 1995  
[IMAGE AVAILABLE]  
APPL-NO: 08/067,684 DATE FILED: May 26, 1993  
REL-US-DATA: Division of Ser. No. 723,617, Jun. 27, 1991, abandoned.

=> d 12 1-21 kwic

US PAT NO: 5,885,796 [IMAGE AVAILABLE] L2: 1 of 21

SUMMARY:

BSUM(21)

Expression of soluble derivatives of cell-surface glycoproteins in the immunoglobulin gene superfamily has been achieved for CD4, the receptor for **HIV-1**, and **CD28** and B7 receptors, using hybrid fusion molecules consisting of DNA sequences encoding amino acids corresponding to portions of the extracellular domain of CD4 receptor fused to **antibody** domains (immunoglobulin .gamma.1 (Capon et al., Nature 337:525-531 (1989) (CD4) and Linsley et al., J. Exp. Med., supra (**CD28** and B7))).

US PAT NO: 5,885,579 [IMAGE AVAILABLE] L2: 2 of 21

SUMMARY:

BSUM(21)

Expression of soluble derivatives of cell-surface glycoproteins in the immunoglobulin gene superfamily has been achieved for CD4, the receptor for **HIV-1**, and **CD28** and B7 receptors, using hybrid fusion molecules consisting of DNA sequences encoding amino acids corresponding to portions of the extracellular domain of CD4 receptor fused to **antibody** domains (immunoglobulin .gamma.1 (Capon et al., Nature 337:525-531 (1989) (CD4) and Linsley et al., J. Exp. Med., supra (**CD28** and B7))).

US PAT NO: 5,883,223 [IMAGE AVAILABLE] L2: 3 of 21

DRAWING DESC:

DRWD(16)

FIG. 15 depicts cell surface staining of CD4.sup.+ T cells obtained from an **HIV** seronegative individual following stimulation (S1, S2 and S3) with an anti-CD3 monoclonal **antibody** and an anti-**CD28** monoclonal **antibody** over days in culture.

DRAWING DESC:

DRWD(17)

FIG. 16 depicts cell surface staining of CD4.sup.+ T cells obtained from an HIV seropositive individual following stimulation (S1, S2 and S3) with an anti-CD3 monoclonal antibody and an anti-CD28 monoclonal antibody over days in culture.

DETDESC:

DETD(114)

Another series of experiments was conducted to determine the expression of various T cell surface markers on cells from HIV seropositive and seronegative individuals expanded according to the procedures described in the previous examples. CD28.sup.+ /CD4.sup.+ T cells were obtained as described herein. In these experiments, the anti-CD3 mAb was labeled with a first label (e.g., rhodamine) and the appropriate second antibody (e.g., anti-CD28, anti-CD4, anti-CD8) was labeled with a second label (e.g., fluorescein). T cells were stimulated with plastic immobilized anti-CD3 mAb and anti-CD28 mAb as described herein and the percent of T cells expressing a variety of cell surface markers at different stimulations. . . . FACS analysis. As shown in FIGS. 15 and 16, the overall cell surface marker distribution on T cells obtained from HIV seropositive and seronegative individuals is approximately the same throughout the stimulation assay. It is noteworthy that the presence of one cell surface marker, CD45RA, which is a marker for naive T cells, declines over the course of CD28 stimulated T cell expansion. In contrast, the percent of T cells expressing the memory T cell surface marker, CD45RO, increases with CD28 stimulation. Thus, T cell expansion through CD28 stimulation preferentially expands memory T cells or converts naive T cells to memory T cells. It should be noted that the decline in the percent of T cells expressing CD28 is an artifact of the experiment due to the presence of anti-CD28 antibody in the T cell culture throughout the assay. The presence of anti-CD28 antibody prevents staining of the CD28 antigen.

US PAT NO: 5,861,490 [IMAGE AVAILABLE]

L2: 4 of 21

DETDESC:

DETD(11)

As . . . the body. The different classes of lymphocytes may be sorted based on the differential expression of cell surface markers using antibodies directed to those cell surface markers and flow cytometry. In yet another embodiment of the invention, described herein, flow cytometry. . . . used to measure cell surface markers expressed on the cell surface of clonal populations of CD8.sup.+ cells derived from asymptomatic HIV-1 infected patients. The clonal cell lines from each of the individual patients varied in their ability to inhibit HIV replication. As indicated in TABLE I a variety of phenotypic markers are displayed within the suppressive and non-suppressive clonal populations. The suppressive clones tended to express activation markers such as HLA-DR, S6FI, CD25 and CD28 to a much higher degree than non-suppressive clones.

DETDESC:

DETD(63)

HIV-1 infected asymptomatic volunteers with CD4+ counts >400 were enrolled for this study. Venous blood was obtained under informed consent from. . . with either phytohemagglutinin (PHA [2.mu.g/ml]; Sigma, St. Louis, Mo.) for CD4+ targets or a combination of anti-CD3 (12F6 [100 ng/ml]; anti-CD28 (100 ng/ml; Becton-Dickinson) antibodies which was used for the CD8.sup.+ effector populations.

DRAWING DESC:

DRWD(16)

FIG. 15 depicts cell surface staining of CD4.sup.+ T cells obtained from an HIV seronegative individual following stimulation (S1, S2 and S3) with an anti-CD3 monoclonal **antibody** and an anti-CD28 monoclonal **antibody** over days in culture.

DRAWING DESC:

DRWD(17)

FIG. 16 depicts cell surface staining of CD4.sup.+ T cells obtained from an HIV seropositive individual following stimulation (S1, S2 and S3) with an anti-CD3 monoclonal **antibody** and an anti-CD28 monoclonal **antibody** over days in culture.

DETDESC:

DETD(114)

Another series of experiments was conducted to determine the expression of various T cell surface markers on cells from HIV seropositive and seronegative individuals expanded according to the procedures described in the previous examples. CD28.sup.+ /CD4.sup.+ T cells were obtained as described herein. In these experiments, the anti-CD3 mAb was labeled with a first label (e.g., rhodamine) and the appropriate second **antibody** (e.g., anti-CD28, anti-CD4, anti-CD8) was labeled with a second label (e.g., fluorescein). T cells were stimulated with plastic immobilized anti-CD3 mAb and anti-CD28 mAb as described herein and the percent of T cells expressing a variety of cell surface markers at different stimulations. . . FACS analysis. As shown in FIGS. 15 and 16, the overall cell surface marker distribution on T cells obtained from HIV seropositive and seronegative individuals is approximately the same throughout the stimulation assay. It is noteworthy that the presence of one cell surface marker, CD45RA, which is a marker for naive T cells, declines over the course of CD28 stimulated T cell expansion. In contrast, the percent of T cells expressing the memory T cell surface marker, CD45RO, increases with CD28 stimulation. Thus, T cell expansion through CD28 stimulation preferentially expands memory T cells or converts naive T cells to memory T cells. It should be noted that the decline in the percent of T cells expressing CD28 is an artifact of the experiment due to the presence of anti-CD28 **antibody** in the T cell culture throughout the assay. The presence of anti-CD28 **antibody** prevents staining of the CD28 antigen.

US PAT NO: 5,851,795 [IMAGE AVAILABLE]

L2: 6 of 21

SUMMARY:

BSUM(21)

Expression of soluble derivatives of cell-surface glycoproteins in the immunoglobulin gene superfamily has been achieved for CD4, the receptor for HIV-1, and CD28 and B7 receptors, using hybrid fusion molecules consisting of DNA sequences encoding amino acids corresponding to portions of the extracellular domain of CD4 receptor fused to **antibody** domains (immunoglobulin .gamma.1 (Capon et al., Nature 337:525-531 (1989) (CD4) and Linsley et al., J. Exp. Med., supra (CD28 and B7)).

US PAT NO: 5,849,793 [IMAGE AVAILABLE]

L2: 7 of 21

DETDESC:

DETD(21)

This example illustrates that compound 59 inhibits **HIV-1** virus replication in acutely infected PBMC cultures activated with anti-CD3 and anti-**CD28** monoclonal **antibodies** (FIGS. 4 and 5). Peripheral blood mononuclear cells were isolated from an uninfected individual and depleted of CD8.sup.+ T lymphocytes using a CD8-specific monoclonal **antibody**, according to the procedure described by Smithgall et al., J. Immunol. 156:2324-2330, 1996. Briefly, the procedure substitutes separation with magnetic beads for complement mediated lysis of **antibody** bound cells. The remaining PBMC fractions were suspended in RPMI culture medium supplemented with 10% heat-inactivated human serum at 2.times.10.sup.6 cells/200 .mu.l. Cells were activated with anti-CD3 mAb (1 .mu.g/ml) together with anti-**CD28** mAb (1 .mu.g/ml) in the presence of various concentrations of compound 59. This form of cell activation specifically targets CD4.sup.+ . . .

DETDESC:

DETD(22)

Cells were pretreated with **antibody** and test compound for 2-3 hours prior to addition of the virus inoculum. The virus used in this experiment, **HIV-1.sub.M1**, is a patient-derived isolate, and was used at approximately MOI=5 TCID.sub.50. After 2 hr incubation for adsorption of virus, the . . . were washed free of the inoculum, and then resuspended again in 200 .mu.l of culture medium supplemented with anti-CD3 and anti-**CD28** mAbs together with varying concentrations of compound 59 (to show a dose-response relationship). Cells were then placed into a U-bottom. . .

US PAT NO: 5,844,095 [IMAGE AVAILABLE]

L2: 8 of 21

SUMMARY:

BSUM(21)

Expression of soluble derivatives of cell-surface glycoproteins in the immunoglobulin gene superfamily has been achieved for CD4, the receptor for **HIV-1**, and **CD28** and B7 receptors, using hybrid fusion molecules consisting of DNA sequences encoding amino acids corresponding to portions of the extracellular domain of CD4 receptor fused to **antibody** domains (immunoglobulin .gamma.1 (Capon et al., Nature 337:525-531 (1989) (CD4) and Linsley et al., J. Exp. Med., supra (CD28 and B7)).

US PAT NO: 5,840,502 [IMAGE AVAILABLE]

L2: 9 of 21

DETDESC:

DETD(56)

A variety of **antibodies** known to those of skill in the art, commercially available or available through cell culture depositories, e.g. the ATCC, Rockville, . . . binding agents depending upon the cell type desired to be isolated or enriched and include, but are not limited to, **antibodies** specific to hematopoietic and lymphoid antigens such as, anti-CD2, anti-CD2R, anti-CD3, anti-CD4, anti-CD5 and anti-CD8 specific for T cells; anti-CD6. . . anti-CD24 specific for B-cells and granulocytes; anti-CD25 and anti-CD26 specific for activated T- and B-cells and activated macrophages; anti-CD27 and anti-**CD28** specific for major T-cell subset; anti-CD30 specific for activated T- and B-cells and Sternberg Reed cells; anti-CD31 specific for platelets, . . . monocytes/macrophages; anti-CDw75 specific for mature B-cells; anti-CD76



specific for mature B-cells and T-cell subset; anti-CD77 specific for follicular center B-cells; **antibodies** to cytokines and growth factors (e.g. IL1-IL13, EGF, IGF-1 and II, TGF- $\alpha$  and  $\beta$ ,  $\alpha$ IFN- $\alpha$  and  $\beta$ , FGF, NGF, CIF, IFN- $\alpha$  and  $\beta$ , CSF's); viral antigens (e.g. Hepatitis B virus envelope proteins or **HIV** envelope proteins), hormones, cellular or tumor associated antigens or markers, adhesion molecules, hemostasis molecules, and endothelial cells.

US PAT NO: 5,837,544 [IMAGE AVAILABLE]

L2: 10 of 21

DETDESC:

DETD(53)

In . . . T cell antigen receptor with the peptide antigen-MHC complex. The second costimulatory signal is provided through the interaction of the **CD28** or CTLA4 proteins on the T cell surface with either the B7-2 or B7 proteins, their counterreceptors on the APC. . . still maintaining antigen specificity. This chimeric receptor will link an ECD which is an antigen binding moiety such as an **antibody** or a viral receptor (e.g., CD4, the receptor for **HIV**) to a proliferation signaling domain which is a component of the IL-2R. One embodiment of the CPR invention would be. . .

US PAT NO: 5,814,519 [IMAGE AVAILABLE]

L2: 11 of 21

DETDESC:

DETD(11)

As . . . the body. The different classes of lymphocytes may be sorted based on the differential expression of cell surface markers using **antibodies** directed to those cell surface markers and flow cytometry. In yet another embodiment of the invention, described herein, flow cytometry. . . used to measure cell surface markers expressed on the cell surface of clonal populations of CD8<sup>sup</sup> cells derived from asymptomatic **HIV-1** infected patients. The clonal cell lines from each of the individual patients varied in their ability to inhibit **HIV** replication. As indicated in TABLE I a variety of phenotypic markers are displayed within the suppressive and non-suppressive clonal populations. The suppressive clones tended to express activation markers such as HLA-DR, S6FI, CD25 and **CD28** to a much higher degree than non-suppressive clones.

DETDESC:

DETD(63)

**HIV-1** infected asymptomatic volunteers with CD4+ counts >400 were enrolled for this study. Venous blood was obtained under informed consent from. . . either phytohemagglutinin (PHA [2  $\mu$ g/ml]; Sigma, St. Louis, Mo.) for CD4+ targets or a combination of anti-CD3 (12F6 [100 ng/ml]; anti-**CD28** (100 ng/ml; Becton-Dickinson) **antibodies** which was used for the CD8<sup>sup</sup> effector populations.

US PAT NO: 5,808,068 [IMAGE AVAILABLE]

L2: 12 of 21

DRAWING DESC:

DRWD(4)

FIG. 3 shows a further analysis of therapeutic efficacy of compound 62 in activated (anti-CD3 and anti-**CD28** monoclonal **antibodies**) peripheral blood mononuclear cell (PBMC) cultures infected with **HIV-1** virus and treated with different concentrations of compound 62 ( $\mu$ M). The assay measures p24 as an index of viral replication and

can be directly correlated to efficacy in treating **HIV** infection. These data show anti-viral efficacy of compound 62 in a dose-response fashion.

DETDESC:

DETD(28)

This example illustrates that compound 62 inhibits **HIV-1** virus replication in acutely infected PBMC cultures activated with anti-CD3 and anti-**CD28** monoclonal **antibodies** (FIG. 3). Peripheral blood mononuclear cells were isolated from an uninfected individual and depleted of CD8.sup.+ T lymphocytes using a CD8-specific monoclonal **antibody**, according to the procedure described by Smithgall et al., J. Immunol. 156:2324-2330, 1996. Briefly, the procedure substitutes separation with magnetic beads for complement-mediated lysis of **antibody**-bound cells. The remaining PBMC fractions were suspended in RPMI culture medium supplemented with 10% heat-inactivated human serum at 2.times.10.sup.6 cells/200 .mu.l. Cells were activated with anti-CD3 mAb (1 .mu.g/ml) together with anti-**CD28** mAb (1 .mu.g/ml) in the presence of various concentrations of compound 62. This form of cell activation specifically targets CD3.sup.+ . . .

DETDESC:

DETD(29)

Cells were pretreated with **antibody** and test compound for 2-3 hours prior to addition of the virus inoculum. The virus used in this experiment, **HIV-1.sub.M1**, is a patient-derived isolate, and was used at an approximate multiplicity of infection (MOI)=5 TCID.sub.50. After 2 hr incubation for. . . cells were washed free of the inoculum, and then resuspended in 200 ml of culture medium supplemented with anti-CD3 and anti-**CD28** mAbs together with various concentrations of compound 62 (to show a dose-response relationship). Cells were then placed into a U-bottom. . .

US PAT NO: 5,807,734 [IMAGE AVAILABLE]

L2: 13 of 21

DETDESC:

DETD(167)

CTLA-4 Ig, a **CD28** homolog, also inhibits anti-CD3 induced **HIV-1** production. CTLA-4 is analogous to **CD28** on T cells in that both of these molecules bind B7 on monocytes (Linsley et al. (1991b), supra). Costimulation (i.e. augmentation of T cell receptor (TCR) signaling by cell surface molecules such as **CD28**, CD2, LFA-1 and others) of **CD28** and TCR has been shown to induce high levels of IL-2 production (R. A. W. Van Lier et al., "Signals Involved in T Cell Activation: T Cell Proliferation Induced Through the Synergistic Action of Anti-**CD28** and Anti-CD2 Monoclonal **Antibodies**," Eur. J. Immunol. 18:167-172 (1988)) and IL-2 mRNA accumulation (Linsley et al. (1991a), supra). To determine what effect blocking of the **CD28/B7** pathway has on **HIV-1** production, soluble recombinant CTLA-4 Ig fusion protein (Linsley et al. (1991b), supra) or mAb to **CD28** (9.3) or B7 (BB1) was added to anti-CD3 activated PBMC in the presence or absence of exogenous IL-2.

DETDESC:

DETD(175)

Table 3 shows that all of the adhesion molecules, except B7/**CD28**, that are important for **HIV-1** production by anti-CD3 activation, are also important for **HIV-1** production following activation by

SAg. However, soluble CTLA-4 Ig did not inhibit **HIV-1** production induced by SAg even in the absence of exogenous IL-2. The lack of inhibition by CTLA-4 Ig in SAg. . . large amounts of IL-2, .gamma.-IFN, and TNF (C. D. Tsoukas et al., "Activation of Resting T Lymphocytes by Anti-CD3 (T3) **Antibodies** in the Absence of Monocytes," J. Immunol. 135:1719-1723 (1985); H. Fischer et al., "Production of TNF-.alpha. and TNF-.beta. by Staphylococcal. . .

US PAT NO: 5,795,572 [IMAGE AVAILABLE]

L2: 14 of 21

DETDESC:

DETD(167)

CTLA-4 Ig, a **CD28** homolog, also inhibits anti-CD3 induced **HIV-1** production. CTLA-4 is analogous to **CD28** on T cells in that both of these molecules bind B7 on monocytes (Linsley et al. (1991b), supra). Costimulation (i.e. augmentation of T cell receptor (TCR) signaling by cell surface molecules such as **CD28**, CD2, LFA-1 and others) of **CD28** and TCR has been shown to induce high levels of IL-2 production (R. A. W. Van Lier et al., "Signals Involved in T Cell Activation: T Cell Proliferation Induced Through the Synergistic Action of Anti-**CD28** and Anti-CD2 Monoclonal **Antibodies**," Eur. J. Immunol. 18: 167-172 (1988)) and IL-2 mRNA accumulation (Linsley et al. (1991a), supra). To determine what effect blocking of the **CD28**/B7 pathway has on **HIV-1** production, soluble recombinant CTLA-4 Ig fusion protein (Linsley et al. (1991b), supra) or mAb to **CD28** (9.3) or B7 (BB1) was added to anti-CD3 activated PBMC in the presence or absence of exogenous IL-2.

DETDESC:

DETD(175)

Table 3 shows that all of the adhesion molecules, except B7/**CD28**, that are important for **HIV-1** production by anti-CD3 activation, are also important for **HIV-1** production following activation by SAg. However, soluble CTLA-4 Ig did not inhibit **HIV-1** production induced by SAg even in the absence of exogenous IL-2. The lack of inhibition by CTLA-4 Ig in SAg. . . large amounts of IL-2, .gamma.-IFN, and TNF (C. D. Tsoukas et al., "Activation of Resting T Lymphocytes by Anti-CD3 (T3) **Antibodies** in the Absence of Monocytes," J. Immunol. 135: 1719-1723 (1985); H. Fischer et al., "Production of TNF-.alpha. and TNF-.beta. by. . .

US PAT NO: 5,770,197 [IMAGE AVAILABLE]

L2: 15 of 21

SUMMARY:

BSUM(20)

Expression of soluble derivatives of cell-surface glycoproteins in the immunoglobulin gene superfamily has been achieved for CD4, the receptor for **HIV-1**, and **CD28** and B7 receptors, using hybrid fusion molecules consisting of DNA sequences encoding amino acids corresponding to portions of the extracellular domain of CD4 receptor fused to **antibody** domains (immunoglobulin .gamma.1 (Capon et al., Nature 337:525-531 (1989) (CD4) and Linsley et al., J. Exp. Med., supra (**CD28** and B7))).

US PAT NO: 5,744,317 [IMAGE AVAILABLE]

L2: 16 of 21

DETDESC:

DETD(61)

In conclusion, the decline in the number of **CD28**.sup.+ T cells with age provides a possible explanation for many of the previous findings on decreased proliferative response to mitogens, reduced delayed-type hypersensitivity response to recall antigens, and diminished **antibody** response to influenza vaccines in the elderly (B. A. Effros (1993), supra). It has been recently shown that in **HIV**+ individuals, there is a strong positive correlation between the lack of **CD28** expression and poor mitogen-induced T cell proliferation. Although the results of this Example do not necessarily explain all types of . . . in immune responsiveness which have been identified, e.g. in vitro stimulation with anti-**CD3** and phorbol esters, a regimen which bypasses **CD28**, they are suggestive of at least one mechanism for changes in immune responsiveness. Nevertheless, if the **CD28**-negative subset were shown to be a predominant factor in proliferative decline, this would be consistent with the previous hypothesis that. . .

US PAT NO: 5,741,899 [IMAGE AVAILABLE]

L2: 17 of 21

DRAWING DESC:

DRWD(58)

In . . . T cell antigen receptor with the peptide antigen-MHC complex. The second costimulatory signal is provided through the interaction of the **CD28** or **CTLA4** proteins on the T cell surface with either the **B7-2** or **B7** proteins, their counterreceptors on the APC. . . still maintaining antigen specificity. This chimeric receptor will link an ECD which is an antigen binding moiety such as an **antibody** or a viral receptor (e.g., **CD4**, the receptor for **HIV**) to a proliferation signaling domain which is a component of the **IL-2R**. One embodiment of the CPR invention would be. . .

US PAT NO: 5,712,149 [IMAGE AVAILABLE]

L2: 18 of 21

SUMMARY:

BSUM(16)

Decreased **CD28** expression in both **CD4** and **CD8** T cell populations from **HIV**-infected individuals correlates with defects in T cell function, tendency to undergo activation-induced apoptosis, and disease progression. Correction of defects in . . . apoptosis (a programmed cell death mechanism initiated by aberrant signal transduction) is observed in vitro when cells are cultured with anti-**CD28 antibodies** (Brinchman et al., J. Inf. Dis. 169:730-738 (1994); Caruso et al., Scand. J. Immunol. 40:485-490 (1994); Landay et al., Clin. . . (1993); Groux et al., J. Exp. Med. 175:331-340 (1992); Meygaard et al., Science 257:217-219 (1992); and Choremi-Papadopoulou et al., J. Aids 7:245-253 (1994)).

DETDESC:

DETD(99)

The . . . introduced into syngeneic mice (Chen et al., J. Exp. Med. supra). **EL-4** cells lack expression of the **B7** ligand for **CD28** and do not elicit protective immunity except by repeated injection of large numbers of irradiated tumor cells (ibid.). In contrast, . . . of existing **EL-4** tumors and confers lasting protective immunity against subsequent injections with **B7**.sup.- **EL-4** cells (ibid.). The ability of **CD28**-based chimeric receptors to augment the immune response to a relatively non-immunogenic tumor is tested in vivo using mice which are . . . whose lymphocytes express high levels of the **CD28-3** receptor were identified by analyzing blood and lymphoid tissue by FACS with **antibodies** to human **CD4**. Such mice will be injected with non-manipulated **EL-4** cells or **EL-4** cells expressing the **HIV** envelope

protein. The ability of these cells to form tumors in CH28-3 transgenic and normal mice is compared. The expectation is that stimulation of the CH28-3 receptor on transgenic T cells by HIV env expressed on the EL-4 cells will stimulate an immune response to EL-4 cells which will be absent in normal. . . of tumors. The non-manipulated EL-4 cells should form tumors in both kinds of mice. These experiments demonstrate the ability of CD28-based chimeric receptors to provide co-stimulation in a situation in which antigen-responsive cells are present, but the natural immune response is. . .

US PAT NO: 5,691,135 [IMAGE AVAILABLE]

L2: 19 of 21

DETDESC:

DETD(9)

Yet another embodiment of the present invention is a method for inhibiting HIV infection of a mammal by identifying a mammal in need of treatment for HIV infection, and administering to the mammal a pharmacologically active compound that suppresses the expression of VH3 immunoglobulins by lymphocytes, whereby HIV infection is inhibited. Preferably, the compound is an immunosuppressive agent, most preferably a kinase inhibitor or cyclosporine. Alternatively, the compound is preferably an anti-receptor **antibody** which binds to a membrane protein. Even more preferably, the **antibody** binds to one of the following antigens: B7, **CD28**, CD72 or CD5. Still even more preferably, the compound is an anticytokine **antibody**, most preferably IL-6 or TGF- $\beta$ .

US PAT NO: 5,686,281 [IMAGE AVAILABLE]

L2: 20 of 21

SUMMARY:

BSUM(16)

Decreased **CD28** expression in both CD4 and CD8 T cell populations from HIV-infected individuals correlates with defects in T cell function, tendency to undergo activation-induced apoptosis, and disease progression. Correction of defects in. . . apoptosis (a programmed cell death mechanism initiated by aberrant signal transduction) is observed in vitro when cells are cultured with anti-**CD28 antibodies** (Brinchman et al., J. Inf. Dis. 169:730-738 (1994); Caruso et al., Scand. J. Immunol. 40:485-490 (1994); Landay et al., Clin. . . (1993); Groux et al., J. Exp. Med, 175:331-340 (1992); Meyaard et al., Science 257:217-219 (1992); and Choremi-Papadopoulou et al., J. Aids 7:245-253 (1994)).

DETDESC:

DETD(99)

The . . . introduced into syngeneic mice (Chen et al., J. Exp. Med. supra). EL-4 cells lack expression of the B7 ligand for **CD28** and do not elicit protective immunity except by repeated injection of large numbers of irradiated tumor cells (ibid.). In contrast, . . . of existing EL-4 tumors and confers lasting protective immunity against subsequent injections with B7.sup.31 EL-4 cells (ibid.). The ability of **CD28**-based chimeric receptors to augment the immune response to a relatively non-immunogenic tumor is tested in vivo using mice which are. . . whose lymphocytes express high levels of the CH28-3 receptor were identified by analyzing blood and lymphoid tissue by FACS with **antibodies** to human CD4. Such mice will be injected with non-manipulated EL-4 cells or EL-4 cells expressing the HIV envelope protein. The ability of these cells to form tumors in CH28-3 transgenic and normal mice is compared. The expectation is that stimulation of the CH28-3 receptor on transgenic T cells by HIV env expressed on the

EL-4 cells will stimulate an immune response to EL-4 cells which will be absent in normal. . . . of tumors. The non-manipulated EL-4 cells should form tumors in both kinds of mice. These experiments demonstrate the ability of **CD28**-based chimeric receptors to provide co-stimulation in a situation in which antigen-responsive cells are present, but the natural immune response is. . . .

US PAT NO: 5,434,131 [IMAGE AVAILABLE]

L2: 21 of 21

SUMMARY:

BSUM(13)

Expression of soluble derivatives of cell-surface glycoproteins in the immunoglobulin gene superfamily has been achieved for CD4, the receptor for **HIV-1**, and **CD28** and B7 receptors, using hybrid fusion molecules consisting of DNA sequences encoding amino acids corresponding to portions of the extracellular domain of CD4 receptor fused to **antibody** domains (immunoglobulin .gamma.1 (Capon et al., Nature 337:525-531 (1989) (CD4) and Linsley et al., J. Exp. Med., supra (**CD28** and B7))).

\*\*\*\*\*  
ENTER PASSWORD:  
p58093fe  
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Welcome to DIALOG

Dialog level 99.07.29D

Last logoff: 16sep99 12:27:09  
Logon file001 16sep99 14:48:39  
F226 - Preliminary Records Through 6/14/99  
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File 1:ERIC 1966-1999/Aug  
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Set	Items	Description
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? b 410

>>>'IALOG' not recognized as set or accession number  
? set hi ;set hi

16sep99 14:48:45	User208760	Session D1319.1
\$0.36	0.110	DialUnits File1
\$0.36	Estimated cost	File1
	FTSNET	0.016 Hrs.
\$0.36	Estimated cost	this search
\$0.36	Estimated total session cost	0.110 DialUnits

File 410:Chronolog(R) 1981-1999 Jul/Aug  
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Set	Items	Description
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HILIGHT set on as ''

**HILIGHT set on as ''**

? begin 5,73,155,399,357

16sep99 14:49:04	User208760	Session D1319.2
\$0.00	0.058	DialUnits File410
\$0.00	Estimated cost	File410
	FTSNET	0.005 Hrs.
\$0.00	Estimated cost	this search
\$0.36	Estimated total session cost	0.168 DialUnits

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File 5:Biosis Previews(R) 1969-1999/Aug W2  
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File 73:EMBASE 1974-1999/Sep W1  
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File 155:MEDLINE(R) 1966-1999/Nov W1  
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File 399:CA SEARCH(R) 1967-1999/UD=13111  
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HELP DERWENT for details.

Set	Items	Description
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? s	(cd28) and (ccr5)	
	8221	CD28
	2167	CCR5
S1	24	(CD28) AND (CCR5)
? rd	s1	
...completed examining records		
	S2	15 RD S1 (unique items)
? t	s2/7/all	

2/7/1 (Item 1 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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11878986 BIOSIS NO.: 199900125095  
Altered expression of CD4, CD54, CD62L, and **CCR5** in primary  
lymphocytes productively infected with the human immunodeficiency virus.

AUTHOR: Marodon Gilles; Landua Nathaniel R; Posnett David N(a)  
AUTHOR ADDRESS: (a)CUMC, 1300 York Ave., Box 56, New York, NY 10021, USA

JOURNAL: AIDS Research and Human Retroviruses 15 (2):p161-171 Jan. 20,  
1999

ISSN: 0889-2229

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Infection of T cells with HIV-1 induces loss of CD4 and HLA class I from the cell surface. In the present article we have investigated whether changes in expression of other cell surface molecules could be related to HIV infection. To detect HIV-infected cells at the single-cell level, peripheral blood lymphocytes were infected in vitro with HIV-HSA, a reporter virus encoding the murine heat-stable antigen. Expression of HSA on activated primary lymphocytes was an efficient indicator of productive infection. Expression of the majority of the cell surface proteins studied was unaffected by HIV infection (HLA class I, II, CD11a, CD18, CD25, CD27, **CD28**, CD29, CD30, CD31, CD38, CD44, CD45R0, CD49d, CD57, CD94, CD95, and CXCR4). However, phenotypic changes specific to the productively infected cells were detected. Expression of the CD4 molecule was progressively lost and this was closely associated with loss of CD62L expression, a molecule involved in T cell homing into the lymph nodes. By contrast, T cells productively infected with this T-tropic reporter virus were enriched for CD54, and for **CCR5**, the main coreceptor for M-tropic viruses. Given the roles of CD62L, CD54, and **CCR5** in lymphocyte trafficking, these results suggest that cells productively infected with HIV might have altered homing patterns in vivo.

2/7/2 (Item 2 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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11699641 BIOSIS NO.: 199800481372  
Naive and memory CD4 T cells differ in their susceptibilities to human  
immunodeficiency virus type 1 infection following **CD28**



costimulation: Implications for transmission and pathogenesis.

AUTHOR: Riley James L; Lete Bruce L; Craighead Nancy; Franco Romano Tara;  
Kim Daniel; Carroll Richard G; June Carl H(a)  
AUTHOR ADDRESS: (a)Mail Stop 061, Naval Med. Res. Inst., 8901 Wisconsin  
Ave., Bethesda, MD 20889-5607, USA

JOURNAL: Journal of Virology 72 (10):p8273-8280 Oct., 1998  
ISSN: 0022-538X  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: In vitro evidence suggests that memory CD4+ cells are preferentially infected by human immunodeficiency virus type 1 (HIV-1), yet studies of HIV-1-infected individuals have failed to detect preferential memory cell depletion. To explore this paradox, we stimulated CD45RA+ CD4+ (naive) and CD45RO+ CD4+ (memory) cells with antibodies to CD3 and **CD28** and infected them with either **CCR5**-dependent (R5) or CXCR4-dependent (X4) HIV-1 isolates. Naive CD4+ cells supported less X4 HIV replication than their memory counterparts. However, naive cells were susceptible to R5 viral infection, while memory cells remained resistant to infection and viral replication. As with the unseparated cells, mixing the naive and memory cells prior to infection resulted in cells resistant to R5 infection and highly susceptible to X4 infection. While both naive and memory CD4+ subsets downregulated **CCR5** expression in response to **CD28** costimulation, only the memory cells produced high levels of the beta-chemokines RANTES, MIP-1alpha-, and MIP-1beta upon stimulation. Neutralization of these beta-chemokines rendered memory CD4+ cells highly sensitive to infection with R5 HIV-1 isolates, indicating that downregulation of **CCR5** is not sufficient to mediate complete protection from **CCR5** strains of HIV-1. These results indicate that susceptibility to R5 HIV-1 isolates is determined not only by the level of **CCR5** expression but also by the balance of **CCR5** expression and beta-chemokine production. Furthermore, our results suggest a model of HIV-1 transmission and pathogenesis in which naive rather than memory CD4+ T cells serve as the targets for early rounds of HIV-1 replication.

2/7/3 (Item 3 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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11623114 BIOSIS NO.: 199800405271  
Maturation of human neonatal CD4+ and CD8+ T lymphocytes into Th1/Th2 effectors.

AUTHOR: Delespesse Guy; Yang Liang Peng; Ohshima Yusei; Demeure Christian;  
Shu Uno; Byun Dae Gyoo; Sarfati M  
AUTHOR ADDRESS: Univ. Montreal, Centre Rech. Louis-Charles Simard, Campus  
Notre-Dame CHUM, 1560 Sherbrooke St. E., M, Canada

JOURNAL: Vaccine 16 (14-15):p1415-1419 Aug.-Sept., 1998  
ISSN: 0264-410X  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The increased susceptibility of neonates to infections has been ascribed to the immaturity of their immune system. More particularly, T cell-dependent responses were shown to be biased towards a Th2 phenotype. Our studies on the in vitro maturation of umbilical cord blood T cells suggest that the Th2 bias of neonatal response cannot be simply ascribed to intrinsic properties of neonatal T cells. Phenotypically, neonatal CD4+ T cells are more immature than their adult CD45RO-/RA+ naive

counterparts and they contain a subset (10-20%) of CD45RO-/RA+ CD31 - cells which is very low in adults and displays some unique functional features. The activation and maturation of neonatal CD4+ T cells is particularly dependent upon the strength of CD28-mediated cosignal which dictates not only the cytokine profile released upon primary activation but also the response to IL-12. Activation of adult as well as neonatal CD4+ T cells in the context of low CD28 costimulation yields to the production of low levels of only one cytokine, ie. IL-2. In contrast, strong CD28 costimulation supports the production of high levels of type 1 (IL-2, IFNgamma and TNFbeta) and low levels of type 2 (IL-4 and IL-13) cytokines by neonatal T cells. The low levels of naive T cell-derived IL-4 are sufficient to support their development into high IL-4/IL-5 producers by an autocrine pathway. The ability of IL-12 to prime neonatal CD4+ T cells for increased production of IL-4 (in addition to IFNgamma) is observed only when CD28 cosignal is minimal. Under optimal activation conditions (i.e. with antiCD3/B7.1 or allogenic dendritic cells) the response and the maturation of neonatal and adult naive T cells are similar. Thus the Th2 bias of neonatal immune response cannot be simply ascribed to obvious intrinsic T cell defect but rather to particular conditions of Ag presentation at priming. Unlike CD4+ T cells, neonatal CD8+ T cells strictly require exogenous IL-4 to develop into IL-4/IL-5 producers. Most importantly, anti-CD3/B7-activated neonatal CD8 T cells coexpress CD4 as well as CCR5 and CXCR4 and are susceptible to HIV-1 infection in vitro.

2/7/4 (Item 4 from file: 5)  
DIALOG(R)File 5:BIOSIS Previews(R)  
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10897567 BIOSIS NO.: 199799518712  
Differential regulation of HIV-1 fusion cofactor expression by CD28 costimulation of CD4+ T cells.

AUTHOR: Carroll Richard G; Riley James L; Levine Bruce L; Feng Yu; Kaushal Sumesh; Ritchey David W; Bernstein Wendy; Weislow Owen S; Brown Charles R ; Berger Edward A; June Carl H(a); St Louis Daniel C  
AUTHOR ADDRESS: (a)Jackson Found. Advancement of Military Med., Rockville, MD 20850, USA

JOURNAL: Science (Washington D C) 276 (5310):p273-276 1997  
ISSN: 0036-8075  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Activation of CD4+ T lymphocytes from human immunodeficiency virus-type 1 (HIV 1)-infected donors with immobilized antibodies to CD3 and CD28 induces a virus resistant state. This effect is specific for macrophage-tropic HIV-1. Transcripts encoding CXCR4/Fusin, the fusion cofactor used by T cell line-tropic isolates, were abundant in CD3/CD28-stimulated cells, but transcripts encoding CCR5, the fusion cofactor used by macrophage-tropic viruses, were not detectable. Thus, CD3/CD28 costimulation induces an HIV-1-resistant phenotype similar to that seen in some highly exposed and HIV-uninfected individuals.

2/7/5 (Item 1 from file: 73)  
DIALOG(R)File 73:EMBASE  
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07492963 EMBASE No: 1998291969  
Chemokines: Understanding their role in T-lymphocyte biology  
Ward S.G.; Westwick J.  
S.G. Ward, Department Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY United Kingdom

AUTHOR EMAIL: prssgw@bath.ac.uk  
Biochemical Journal ( BI OCHEM. J. ) (United Kingdom) 01 1998, 333/3  
(457-470)

CODEN: BIJOA ISSN: 0264-6021  
DOCUMENT TYPE: Journal; Review  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH  
NUMBER OF REFERENCES: 175

The chemokines are a complex superfamily of small, secreted proteins that were initially characterized through their chemotactic effects on a variety of leucocytes. The superfamily is divided into families based on structural and genetic considerations and have been termed the CXC, CC, C and CXinf 3C families. Chemokines from these families have a key role in the recruitment and function of T lymphocytes. Moreover, T lymphocytes have also been identified as a source of a number of chemokines. T lymphocytes also express most of the known CXC and CC chemokine receptors to an extent that depends on their state of activation/differentiation and/or the activating stimuli. The expression of two chemokine receptors, namely CXCR4 and CCR5, together with the regulated production of their respective ligands, appears to be extremely important in determining sensitivity of T cells to HIV-1 infection. The intracellular events which mediate the effects of chemokines, particularly those elicited by the CC chemokine RANTES, include activation of both G-protein- and protein tyrosine kinase-coupled signalling pathways. The present review describes our current understanding of the structure and expression of chemokines and their receptors, the effects of chemokines on T-cell function(s), the intracellular signalling pathways activated by chemokines and the role of certain chemokines and chemokine receptors in determining sensitivity to HIV-1 infection.

2/7/6 (Item 2 from file: 73)  
DIALOG(R)File 73:EMBASE  
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07377738 EMBASE No: 1998265163  
Maturation of human neonatal CD4sup + and CD8sup + T lymphocytes into Th1/Th2 effectors  
Delespesse G.; Liang Peng Yang; Ohshima Y.; Demeure C.; Shu U.; Dae Gyoo Byun; Sarfati M.  
G. Delespesse, University of Montreal, Ctr. de Rech. Louis-Charles Simard, Campus Notre-Dame du CHUM, 1560 Sherbrooke Street East, Montreal, Que. H2L 4M1 Canada  
AUTHOR EMAIL: Delespesse@ere.UMontreal.ca  
Vaccine ( VACCINE ) (United Kingdom) 1998, 16/14-15 (1415-1419)

CODEN: VACCD ISSN: 0264-410X  
PUBLISHER ITEM IDENTIFIER: S0264410X98001017  
DOCUMENT TYPE: Journal; Conference Paper  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH  
NUMBER OF REFERENCES: 37

The increased susceptibility of neonates to infections has been ascribed to the immaturity of their immune system. More particularly, T cell-dependent responses were shown to be biased towards a Th2 phenotype. Our studies on the in vitro maturation of umbilical cord blood T cells suggest that the Th2 bias of neonatal response cannot be simply ascribed to intrinsic properties of neonatal T cells. Phenotypically, neonatal CD4sup + T cells are more immature than their adult CD45ROsup -/RASup + naive counterparts and they contain a subset (10-20%) of CD45ROsup -/RASup + CD3lsup - cells which is very low in adults and displays some unique functional features. The activation and maturation of neonatal CD4sup + T cells is particularly dependent upon the strength of CD28- mediated cosignal which dictates not only the cytokine profile released upon primary activation but also the response to IL-12. Activation of adult as well as

neonatal CD4sup + T cells in the context of low CD28 costimulation yields to the production of low levels of only one cytokine i.e. IL-2. In contrast, strong CD28 costimulation supports the production of high levels of type 1 (IL-2, IFNgamma and TNFbeta) and low levels of type 2 (IL-4 and IL-13) cytokines by neonatal T cells. The low levels of naive T cell-derived IL-4 are sufficient to support their development into high IL-4/IL-5 producers by an autocrine pathway. The ability of IL-12 to prime neonatal CD4sup + T cells for increased production of IL-4 (in addition to IFNgamma) is observed only when CD28 cosignal is minimal. Under optimal activation conditions (i.e. with anti-CD3/B7.1 or allogenic dendritic cells) the response and the maturation of neonatal and adult naive T cells are similar. Thus the Th2 bias of neonatal immune response cannot be simply ascribed to obvious intrinsic T cell defect but rather to particular conditions of Ag presentation at priming. Unlike CD4sup + T cells, neonatal CD8sup + T cells strictly require exogenous IL-4 to develop into IL-4/IL-5 producers. Most importantly, anti-CD3/B7-activated neonatal CD8sup + T cells coexpress CD4 as well as CCR5 and CXCR4 and are susceptible to HIV-1 infection in vitro.

2/7/7 (Item 3 from file: 73)  
DIALOG(R)File 73:EMBASE  
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07343011 EMBASE No: 1998251870

The role of co-stimulation in regulation of chemokine receptor expression and HIV-1 infection in primary T lymphocytes

Carroll R.G.; Riley J.L.; Levine B.L.; Blair P.J.; Louis D.C.St.; June C.H.

R.G. Carroll, Henry M. Jackson Foundation, Military HIV Research Program, Bethesda, MD 20889 United States  
Seminars in Immunology ( SEMIN. IMMUNOL. ) (United Kingdom) 1998, 10/3 (195-202)

CODEN: SEIME ISSN: 1044-5323  
DOCUMENT TYPE: Journal; Article  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH  
NUMBER OF REFERENCES: 50

Fusion and entry of the human immunodeficiency virus (HIV) into CD4sup + T lymphocytes requires expression of CD4 and a coreceptor. At least eight chemokine receptors can serve as coreceptors for HIV. Accumulating evidence indicates that multiple factors, including the state of cellular differentiation and activation, regulate the expression of alpha- and beta-chemokine receptors on lymphocytes. For example, binding of antibodies to the CD28 coreceptor can downregulate expression of beta-chemokine receptors, and this appears to have important consequences on the susceptibility of CD4sup + T lymphocytes to infection by HIV-1. In contrast, binding of the natural CD28 ligand B7 or antibodies to the CD28 homologue CTLA-4 can upregulate CCR5 expression, suggesting a reciprocal interaction between CD28 and CTLA-4 and the regulation of beta-chemokine receptor expression. Thus, the CD28/CTLA-4/B7 co-stimulation pathway is identified as a potential novel target for the control of susceptibility to some strains of HIV-1 infection.

2/7/8 (Item 4 from file: 73)  
DIALOG(R)File 73:EMBASE  
(c) 1999 Elsevier Science B.V. All rts. reserv.

06838931 EMBASE No: 1997121441

Differential regulation of HIV-1 fusion cofactor expression by CD28 costimulation of CD4sup + T cells

Carroll R.G.; Riley J.L.; Levine B.L.; Feng Y.; Kaushal S.; Ritchey D.W.; Bernstein W.; Weislow O.S.; Brown C.R.; Berger E.A.; June C.H.; St. Louis D.C.

C.H. June, Advancement of Military Medicine, Rockville, MD 20850 United States

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Science ( SCIENCE ) (United States) 1997, 276/5310 (273-276)

CODEN: SCIEA ISSN: 0036-8075

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 22

Activation of CD4sup + T lymphocytes from human immunodeficiency virus-type 1 (HIV-1)-infected donors with immobilized antibodies to CD3 and **CD28** induces a virus-resistant state. This effect is specific for macrophage-tropic HIV-1. Transcripts encoding CXCR4/Fusin, the fusion cofactor used by T cell line-tropic isolates, were abundant in CD3/**CD28**-stimulated cells, but transcripts encoding **CCR5**, the fusion cofactor used by macrophage-tropic viruses, were not detectable. Thus, CD3/**CD28** costimulation induces an HIV-1-resistant phenotype similar to that seen in some highly exposed and HIV-uninfected individuals.

2/7/9 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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09753005 99057046

Lymphocyte-specific chemokine receptor CXCR3: regulation, chemokine binding and gene localization.

Loetscher M; Loetscher P; Brass N; Meese E; Moser B

Theodor-Kocher Institute, University of Bern, Switzerland.

Eur J Immunol (GERMANY) Nov 1998, 28 (11) p3696-705, ISSN 0014-2980

Journal Code: EN5

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Expression of CXCR3, the receptor for the CXC chemokines IFN-gamma-inducible 10-kDa protein (IP10) and monokine induced by IFN-gamma (Mig), in human T lymphocytes and their responses to IP10 and Mig were analyzed. About 40 % of resting T lymphocytes (and low numbers of B cells and natural killer cells) stained positive for CXCR3 but these cells did not express CXCR3 transcripts and did not respond to these chemokines. However, treatment with IL-2 with or without addition of phytohemagglutinin for 10 or more days resulted in cultures of fully responsive, CXCR3-positive T lymphocytes. Treatment with anti-CD3 antibodies in the presence or absence of soluble anti-**CD28** antibodies was inhibitory. Addition of chondroitin sulfate C to CXCR3-expressing murine pre-B cells allowed the determination of high-affinity binding for Mig and IP10 with Kd of 0.9-1.2 nM and 0.2-0.3 nM, respectively, and  $1.3 \times 10^4$  binding sites per cell. The gene for CXCR3 was localized on human chromosome Xq13 which is in clear contrast to all other chemokine receptor genes, suggesting unique function(s) for this receptor and its ligands that may lie beyond their established role in T cell-dependent immunity.

2/7/10 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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09653035 98406235

Naive and memory CD4 T cells differ in their susceptibilities to human immunodeficiency virus type 1 infection following **CD28** costimulation: implicatip6s for transmission and pathogenesis.

Riley JL; Levine BL; Craighead N; Francomano T; Kim D; Carroll RG; June CH

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Languages: ENGLISH

Document type: JOURNAL ARTICLE

In vitro evidence suggests that memory CD4(+) cells are preferentially infected by human immunodeficiency virus type 1 (HIV-1), yet studies of HIV-1-infected individuals have failed to detect preferential memory cell depletion. To explore this paradox, we stimulated CD45RA+ CD4(+) (naive) and CD45RO+ CD4(+) (memory) cells with antibodies to CD3 and **CD28** and infected them with either **CCR5**-dependent (R5) or CXCR4-dependent (X4) HIV-1 isolates. Naive CD4(+) cells supported less X4 HIV replication than their memory counterparts. However, naive cells were susceptible to R5 viral infection, while memory cells remained resistant to infection and viral replication. As with the unseparated cells, mixing the naive and memory cells prior to infection resulted in cells resistant to R5 infection and highly susceptible to X4 infection. While both naive and memory CD4(+) subsets downregulated **CCR5** expression in response to **CD28** costimulation, only the memory cells produced high levels of the beta-chemokines RANTES, MIP-1alpha, and MIP-1beta upon stimulation. Neutralization of these beta-chemokines rendered memory CD4(+) cells highly sensitive to infection with R5 HIV-1 isolates, indicating that downregulation of **CCR5** is not sufficient to mediate complete protection from **CCR5** strains of HIV-1. These results indicate that susceptibility to R5 HIV-1 isolates is determined not only by the level of **CCR5** expression but also by the balance of **CCR5** expression and beta-chemokine production. Furthermore, our results suggest a model of HIV-1 transmission and pathogenesis in which naive rather than memory CD4(+) T cells serve as the targets for early rounds of HIV-1 replication.

2/7/11 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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09610215 98361296

Chemokines and T lymphocytes: more than an attraction.

Ward SG; Bacon K; Westwick J

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Immunity (UNITED STATES) Jul 1998, 9 (1) p1-11, ISSN 1074-7613

Journal Code: CCF

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

(82 Refs.)

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09466587 98208263

Cloning and analysis of the promoter region of **CCR5**, a coreceptor for HIV-1 entry.

Moriuchi H; Moriuchi M; Fauci AS

Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

J Immunol (UNITED STATES) Dec 1 1997, 159 (11) p5441-9, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The chemokine receptor **CCR5** is a cofactor for cellular entry of macrophage-tropic strains of HIV-1. Expression of **CCR5** is restricted to T cells, macrophages, and certain cell lines; however, the mechanisms controlling its expression remain largely unknown. To delineate these mechanisms, approximately 1.0 kb of DNA from the immediate 5' upstream

region of CCR5 was cloned and characterized. CCR5 promoter activity was up-regulated by PMA, and a region spanning -417 to +61 relative to the transcription start site was sufficient for the basal and induced activity. DNase I footprinting assays demonstrated several protected areas within this region, and gel shift assays determined binding sites for transcriptional factors Oct-1, Oct-2, T cell factor 1alpha, and GATA1. CCR5 promoter activity was also induced by IL-2 or anti-CD3 Ab, while stimulation with anti-CD28 Ab markedly reduced CD3-mediated up-regulation of the CCR5 promoter. Flow cytometry confirmed the findings at the level of cell surface expression. Further delineation of the regulation of the CCR5 promoter will be important for a more comprehensive understanding of the pathogenesis of HIV disease.

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DIALOG(R) File 399:CA SEARCH(R)  
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130266263 CA: 130(20)266263j JOURNAL  
Direct analysis of viral-specific CD8+ T cells with soluble HLA-A2/tax11-19 tetramer complexes in patients with human T cell lymphotropic virus-associated myelopathy  
AUTHOR(S): Bieganowska, Katarzyna; Hollsberg, Per; Buckle, Guy J.; Lim, Dong-Gyun; Greten, Tim F.; Schneek, Jonathan; Altman, John D.; Jacobson, Steven; Ledis, Stephen L.; Hanchard, Barrie; Chin, Jonathan; Morgan, Owen; Roth, Patricia A.; Hafler, David A.  
LOCATION: Center for Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA  
JOURNAL: J. Immunol. DATE: 1999 VOLUME: 162 NUMBER: 3 PAGES: 1765-1771 CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English PUBLISHER: American Association of Immunologists  
SECTION:  
CA215008 Immunochimistry  
IDENTIFIERS: T cell HLA A2 Tax protein HTLV virus myelopathy  
DESCRIPTORS:  
CD28(antigen)... CD45RA(antigen)... CD45RO(antigen)... CD80(antigen)... CD8-positive T cell... HLA-A2 antigen... Human T-lymphotropic virus 1... Interleukin 2 receptor .beta.-chain... Tax protein... TCR .alpha..beta.(receptor)... Tropical spastic paraparesis...  
activation state, chemokine receptor expression, and TCR usage by HLA-A2-restricted T-cells recognizing Tax epitope in humans with HTLV-I-assocd. myelopathy  
Interleukin 8 receptors...  
.alpha.; activation state, chemokine receptor expression, and TCR usage by HLA-A2-restricted T-cells recognizing Tax epitope in humans with HTLV-I-assocd. myelopathy  
Interleukin 8 receptors...  
.beta.; activation state, chemokine receptor expression, and TCR usage by HLA-A2-restricted T-cells recognizing Tax epitope in humans with HTLV-I-assocd. myelopathy  
Chemokine receptors...  
.beta. chemokine receptor CCR2; activation state, chemokine receptor expression, and TCR usage by HLA-A2-restricted T-cells recognizing Tax epitope in humans with HTLV-I-assocd. myelopathy  
Cytokine receptors...  
.beta. chemokine receptor CCR5; activation state, chemokine receptor expression, and TCR usage by HLA-A2-restricted T-cells recognizing Tax epitope in humans with HTLV-I-assocd. myelopathy  
C-C chemokines...  
.beta., receptor CCR2; activation state, chemokine receptor expression, and TCR usage by HLA-A2-restricted T-cells recognizing Tax epitope in humans with HTLV-I-assocd. myelopathy  
Chemokines...  
.beta., receptor CCR5; activation state, chemokine receptor expression, and TCR usage by HLA-A2-restricted T-cells recognizing Tax epitope in humans with HTLV-I-assocd. myelopathy

Chemokine receptors...

CXCR-3; activation state, chemokine receptor expression and TCR usage  
by HLA-A2-restricted T-cells recognizing Tax epitope in humans with  
HTLV-I-assocd. myelopathy

RANTES(chemokine)...

formation by HLA-A2-restricted T-cells recognizing Tax epitope in  
humans with HTLV-I-assocd. myelopathy

Genes(animal)...

TCRB; activation state, chemokine receptor expression, and TCR usage by  
HLA-A2-restricted T-cells recognizing Tax epitope in humans with  
HTLV-I-assocd. myelopathy

2/7/14 (Item 2 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

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130205815 CA: 130(16)205815u JOURNAL

Functional analysis of the proximal CCR5 promoter

AUTHOR(S): Liu, Rong; Zhao, Xiuqing; Gurney, Theresa A.; Landau,

Nathaniel R.

LOCATION: Aaron Diamond AIDS Research Center, New York, NY, 10016, USA

JOURNAL: AIDS Res. Hum. Retroviruses DATE: 1998 VOLUME: 14 NUMBER: 17

PAGES: 1509-1519 CODEN: ARHRE7 ISSN: 0889-2229 LANGUAGE: English

PUBLISHER: Mary Ann Liebert, Inc.

SECTION:

CA203004 Biochemical Genetics

CA215XXX Immunochemistry

IDENTIFIERS: human gene CCR5 promoter Pd region sequence functional  
analysis, chemokine receptor CCR5 gene transcriptional regulation NFkappaB,  
elements human gene CCR5 promoter Pd region

DESCRIPTORS:

Cytokine receptors...

.beta. chemokine receptor CCR5; functional anal. of the CCR5 gene  
(receptor for CC chemokines) proximal promoter, minimal CCR5 promoter  
Pd localized to region -189 to +36 of the CCR5 receptor gene

Chemokines...

.beta., receptor CCR5; functional anal. of the CCR5 gene (receptor for  
CC chemokines) proximal promoter, minimal CCR5 promoter Pd localized to  
region -189 to +36 of the CCR5 receptor gene

Genes(animal)...

CCR5; functional anal. of the CCR5 gene (receptor for CC chemokines)  
proximal promoter

Genetic elements...

CD28RE, consensus response element for CD28 signaling; functional anal.  
of the CCR5 gene proximal promoter, importance of CD28RE, TATA element,  
NF-.kappa.B-, and AP-1-, and STAT-binding sites

DNA sequences... Transcription initiation site(genetic element)...

functional anal. of the CCR5 gene (receptor for CC chemokines) proximal  
promoter, minimal CCR5 promoter Pd localized to region -189 to +36 of  
the CCR5 receptor gene

AP-1 site(genetic element)... NF-.kappa.B site(genetic element)...

NF-.kappa.B... TATA box(genetic element)... Transcriptional regulation...

functional anal. of the CCR5 gene proximal promoter, importance of TATA  
element, NF-.kappa.B-, and AP-1-, and STAT-binding sites

Intron(genetic element)... Negative regulatory element...

identification of two regions (a 1.9-kb intron and nucleotides -988 to  
-588) that appear to contain neg. transcription elements

Promoter(genetic element)...

Pd; functional anal. of the CCR5 gene (receptor for CC chemokines)  
proximal promoter, minimal CCR5 promoter Pd localized to region -189 to  
+36 of the CCR5 receptor gene

Genetic elements...

transcription factor STAT-binding site; functional anal. of the CCR5  
gene proximal promoter, importance of TATA element, NF-.kappa.B-, and  
AP-1-, and STAT-binding sites



CAS REGISTRY NUMBERS:

220916-02-9 nucleotide sequence; functional anal. of the CCR5 gene  
(receptor for CC chemokines) proximal promoter, minimal CCR5 promoter  
Pd localized to region -189 to +36 of the CCR5 receptor gene

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DIALOG(R)File 399:CA SEARCH(R)

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130037213 CA: 130(4)37213a JOURNAL

Costimulation of naive CD8+ lymphocytes induces CD4 expression and allows human immunodeficiency virus type 1 infection

AUTHOR(S): Kitchen, Scott G.; Korin, Yael D.; Roth, Michael D.; Landay, Alan; Zack, Jerome A.

LOCATION: Division of Hematology-Oncology, UCLA School of Medicine, Los Angeles, CA, 90095, USA

JOURNAL: J. Virol. DATE: 1998 VOLUME: 72 NUMBER: 11 PAGES: 9054-9060

CODEN: JOVIAM ISSN: 0022-538X LANGUAGE: English PUBLISHER: American Society for Microbiology

SECTION:

CA215008 Immunochemistry

IDENTIFIERS: CD8 T cell HIV infection CD4

DESCRIPTORS:

Cytokine receptors...

.beta. chemokine receptor CCR5; CD3/CD28 costimulation of naive CD8+ T-cells induces CD4 expression, allows HIV infection, and induces expression of

Chemokines...

.beta., receptor CCR5; CD3/CD28 costimulation of naive CD8+ T-cells induces CD4 expression, allows HIV infection, and induces expression of

Fetus...

CD3/CD28 costimulation of fetal CD8+ T-cells induces CD4 expression and allows human immunodeficiency virus type 1 infection

CD28(antigen)... CD4(antigen)... CD8-positive T cell... Human immunodeficiency virus 1... T cell activation... TCR-CD3 complex... Viral infection...

CD3/CD28 costimulation of naive CD8+ T-cells induces CD4 expression and allows human immunodeficiency virus type 1 infection

Newborn...

CD3/CD28 costimulation of umbilical cord CD8+ T-cells induces CD4 expression and allows human immunodeficiency virus type 1 infection

T cell infection...

CD4-pos. T cell; CD3/CD28 costimulation of naive CD8+ T-cells induces CD4 expression and allows human immunodeficiency virus type 1 infection

Cytokine receptors...

chemokine, fusin; CD3/CD28 costimulation of naive CD8+ T-cells induces CD4 expression, allows HIV infection, and induces expression of

Dendritic cell...

dendritic cell costimulation of naive CD8+ T-cells induces CD4 expression and allows human immunodeficiency virus type 1 infection

CD4-positive T cell...

infection; CD3/CD28 costimulation of naive CD8+ T-cells induces CD4 expression and allows human immunodeficiency virus type 1 infection